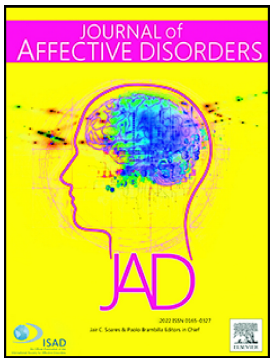
Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.



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Association of mental health with clinical outcomes in hospitalized patients with moderate COVID-19

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ABSTRACT

Objective To assess the association of depression and anxiety with clinical outcomes and laboratory markers among hospitalized patients with coronavirus disease 2019 (COVID-19).

Methods A prospective cohort study in Wuhan, China was conducted in 205 adult hospitalized patients with a diagnosis of moderate coronavirus disease from admission through discharge or death. Anxiety and depression were assessed using the Hospital Anxiety and Depression Scale (HADS). The primary outcome was the incidence of severe or critical COVID-19, and the secondary outcomes were increased length of hospital stay and altered laboratory markers during follow up.

Results Among the 205 hospitalized patients (mean age 58 years; 51.7% male), 25 (12.2%) developed severe or critical COVID-19. According to the HADS scores, 51 (24.9%) and 92 (44.9%) of participants presented with clinically significant anxiety and depression, respectively. Using multi-variable adjusted Cox regression analysis, the adjusted hazard ratio of developing severe or critical COVID-19 associated with anxiety and depression was 1.55 (95% CI: 0.63, 3.80) and 4.28 (95% CI: 1.20, 15.30), respectively. The risk of developing severe or critical COVID-19 with both anxiety and depression was more than four times higher than in patients without anxiety or depression (HR, 4.05; 95% CI: 1.02, 16.00). In addition, both the trends of depression and anxiety were positively associated with a prolonged duration of hospitalization, and immune response was significantly decreased in patients with depression than those without.

Conclusions In patients having coronavirus disease, depression was associated with worse clinical outcomes. These findings highlight the importance of prevention and management of mental health problems in confronting the COVID-19 pandemic.

Keywords: anxiety, depression, COVID-19, epidemiology

INTRODUCTION

The pandemic of coronavirus disease 2019 (COVID-19), first reported in Wuhan, China in the late December of 2019, is caused by a novel coronavirus identified and named as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).(Zhu et al., 2020) By May 18, 2021, over 162 million confirmed COVID-19 cases and 3.4 million deaths from COVID-19 have been reported worldwide.(World Health Organization) Until now, no specific treatment has been proven to be effective for COVID-19. Supportive care, such as oxygen supply in mild and moderate cases and extracorporeal membrane oxygenation for the critically ill patients, is being used.(Chen et al., 2020) Although the case fatality rate among mild to moderate cases was low,(Novel Coronavirus Pneumonia Emergency Response Epidemiology Team, 2020; Wu and McGoogan, 2020) the case fatality rate was as high as 49.0% in critical cases according to a report from China.(Wu and McGoogan, 2020) As an event unprecedented in recent times, and completely new in a global, interconnected world, the COVID-19 pandemic poses numerous challenges, including identify risk factors that are related to clinical progression of COVID-19.

Apart from physical suffering, in-patients with confirmed COVID-19 have been reported to suffer from great psychological pressure including fear of severe disease consequences.(Xiang et al., 2020) They may experience loneliness, denial, anxiety, depression, insomnia, and despair during treatment in isolation ward, which may lower treatment efficacy.(Li et al., 2020) Previous studies suggested that the receipt of psychological treatment is associated with positive recovery rates and a reduction of

physical healthcare use.(Gruber et al., 2022; Jeremy A. Chiles, 2006)

Some studies have reported the prevalence of anxiety and depression in patients with COVID-19 during the hospitalization or convalescence.(Yuan et al., 2020; Zhang et al., 2020) However, limited studies have investigated the mental health status in patients with COVID-19 and longitudinal impact of the progression of illness,(Evans et al., 2021) and the study subjective were patients discharged from hospital. The current study aimed to assess the associations of depression and anxiety with clinical outcomes among hospitalized patients with COVID-19

MATERIAL AND METHODS

A prospective cohort study was conducted of adults with a diagnosis of moderate coronavirus disease who were hospitalized at a major hospital in Wuhan, located in central China. This hospital was a designated center for treating patients with COVID-19. Case definitions of confirmed human infection with SARS-CoV-2 were in accordance with interim guidance from the World Health Organization. (WHO) From January 6 to March 9, 2020, 207 patients who were admitted were enrolled in a prospective cohort study, having met the following criteria: laboratory confirmation of SARS-CoV-2 infection, fever and respiratory tract symptoms, manifestations of pneumonia found on imaging and clinically diagnosed as having a moderate case of COVID-19 at time of admission. Adults who had fever, respiratory symptom and signs of pneumonia in lung imaging were classified as moderate cases.(2020)

Written informed consent was obtained and participants could withdraw from the

study at any time without prejudice. Due to the highly contagious nature of this disease, participants were asked to self-complete online questionnaires or were interviewed by phone in 1~2 days after their hospitalization, and a researcher recorded participants' responses to the questionnaire. Participants were followed through their hospitalization until the last participant was discharged on March 30, 2020. One participant died prior to completing the questionnaire and one refused to participate. A total of 205 questionnaires were completed and included in the analysis.

The study was conducted according to the latest version of the Declaration of Helsinki ethical standards and approved by the Ethical Committee of the Hubei Provincial Hospital of Integrated Chinese (ethical approval code: 2020014).

Measures

Anxiety and depression were assessed by the Hospital Anxiety and Depression Scale (HADS).(Zigmond and Snaith, 1983) HADS consists of seven items measuring anxiety and seven items measuring depression, which are summed to form anxiety and depression subscale scores (HADS-A and HADS-D, respectively). All items are measured on a four-point scale (0-3) and refer to the past week. Total score of either subscale is ranging from 0 to 21. Patients with a score ≥8, on either subscale, was considered to have clinically significant anxiety or depression. We chose the HADS because of its utility in detecting psychiatric symptoms in patients with general medical problems(Bienvenu et al., 2018). The assessment was conducted in the 1~2 days after their hospitalization.

Clinical outcomes and laboratory measurement

In this study, the primary outcome was the incidence of severe or critical cases of COVID-19. Information of clinical, laboratory, treatment, and outcomes were extracted from medical records according modified WHO/International Severe Acute Respiratory and Emerging Infection Consortium case record forms. SARS-CoV-2 in nasopharyngeal swab specimens was detected by real-time RT-PCR (DAAN Gene, China). According to the Chinese management guideline for COVID-19 (version 7) (2020), the illness severity of COVID-19 was defined. Adults who met any of the following criteria were classified as severe cases: (a) respiratory rate ≥ 30 breaths/min; (b) oxygen saturation ≤ 93% at a rest state; (c) arterial partial pressure of oxygen (PaO2)/oxygen concentration (FiO2) ≤ 300 mmHg; (d) > 50% lesions progression within 24 to 48 hours in lung imaging. Adults who meet any of the following criteria were classified as critical cases: (a) occurrence of respiratory failure requiring mechanical ventilation; (b) presence of shock; (c) other organ failure that requires monitoring and treatment in the ICU. Throat-swab specimens were obtained for SARS-CoV-2 RT-PCR re-examination every other day after clinical remission of symptoms. The discharge criteria were as follows: (a) normal temperature for 3 consecutive days; (b) symptom relief; (c) negative throat-swab specimens repeated twice with at least 1 day interval; and (d) significant improvement in exudative lesions in lung imaging. laboratory testing data among the patients were also extracted from medical records. Laboratory markers were tracked from admission to discharge

or death.

Assessment of covariates

Socio-demographic characteristics were collected using a predesigned questionnaire. Frequency of physical activity was categorized as never, sometimes (20+ minutes exercise, 2~4 times a week) and always (20+ minutes exercise, >5 times a week). Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters (kg/m^2, < 23.9, 24.0-27.9, ≥ 28.0).(Chen et al., 2004) Sleep quality was assessed using the Pittsburgh Sleep Quality Index (PSQI) (Buysse et al., 1989), which is a self-administered scale consisting of 18 items regarding sleep over the past month. A higher score indicates poor sleep quality.

Statistical analysis

Continuous variables were expressed as mean (standard division) for variables with normal distribution or median (interquartile range [IQR]) for variables with skewed distribution, and they were compared using ANOVA test (normal distribution) or Kruskal Wallis test (skewed distribution). Categorical variables were summarized as n (%) and compared using Chi-square test or Fisher exact test when needed. The association of anxiety and depression with the risk of developing severe or critical COVID-19 was estimated using Cox proportional hazards regression models with the following covariates: age, sex, education, smoking, alcohol intake, physical activity, BMI, hypertension, diabetes, CVD, and sleep quality. Follow up time was calculated

as the difference between the admission date and the date of confirming severe case or the discharge date. Smoothing splines were generated by generalized additive models to present the association of anxiety and depression symptoms with duration of hospital stay after adjustment for age, sex, education, sleep quality, smoking, alcohol intake, physical activity, BMI, hypertension, diabetes, and CVD. All analyses were performed using SAS 9.4 and R software (The R Foundation, http://www.r-project.org, version 3.6.1). A two-tailed *p* value below 0.05 was considered statistically significant.

RESULTS

Among the 205 hospitalized patients (mean age 58 years; 106 [51.7%] were male) with moderate COVID-19 at admission, 25 (12.2%) developed severe or critical COVID-19 during the follow-up. Eventually, 3 died during hospitalization. The mean of HADS-A and HADS-D scores among the included patients was 5.0 ± 3.2 and 6.3 ± 4.1, respectively. According to the HADS scores, 51 (24.9%) and 92 (44.9%) hospitalized patients presented clinically significant anxiety and depression respectively. Patients who had anxiety were more likely to have lower frequency of physical activity before the infection. Patients who had depression were more likely to have lower education level and poor sleep quality (**Table 1)**.

In the multivariable Cox regression models (model 3), depression was associated with higher risk of developing severe or critical COVID-19 (hazard ratio [HR], 4.28; 95% CI: 1.20, 15.30) (**Figure 2 and sTable 2**). However, there is no statistical

significance of the associations of anxiety with the risk of developing severe or critical COVID-19 (HR, 1.55; 95% CI: 0.63, 3.80) in model 3. The risk of developing severe or critical COVID-19 in patients with both anxiety and depression was more than 4 times higher in patients with neither anxiety nor depression (HR, 4.05; 95% CI: 1.02, 16.00). In addition, scores of HADS-A and HADS-D were both positively associated with the duration of hospital stay (**Figure 1**).

In terms of laboratory findings, WBC, Neutrophil percentage, NLR, CRP, erythrocyte sedimentation rate, D-dimer, LD and inflammatory cytokines (including IL-6 and IL-10) were significantly higher in patients with depression at baseline, while lymphocyte percentage and T cells count were significantly lower. However, the differences of laboratory findings except natural killer cells were not significant between patients with and without anxiety (**Table 2**).

DISCUSSION

To our knowledge, this is the first prospective cohort study to examine the association of depression and anxiety with clinical outcomes and laboratory markers among adult hospitalized patients with COVID-19. Our findings showed that 51 (24.9%) and 92 (44.9%) hospitalized patients presented anxiety and depression respectively, both depression and anxiety were positively associated with a prolonged duration of hospital stay, and depression was independently associated with a higher risk of developing severe or critical COVID-19. The risk of developing severe or critical COVID-19 in patients with both anxiety and depression was more than 4

times higher in patients with neither anxiety nor depression.

Hitherto, some published studies have investigated the prevalence of anxiety and depression among patients with COVID-19. A cross-sectional study posted on preprint demonstrated that 34.72% and 28.47% patients of 144 participants with COVID-19 had anxiety or depression by HADS, respectively.(Kong et al., 2020) The prevalence of depression and anxiety were found in patients newly recovery from COVID-19 infection were 29.2% and 20.8%, respectively (Zhang et al., 2020) A study among cured COVID-19 patients showed that during the convalescent period, self-reported depression appear 42 out of 96 (43.8%).(Yuan et al., 2020) Compared with these studies, our study demonstrated a higher prevalence of depression and anxiety, and the differences could be attributed to different severity of cases, illness phrase and measurements.

Behavioral and emotional changes, including mood disturbance, are considered part of the normal response to acute infection.(Vollmer-Conna, 2001) Nevertheless, an excessive or prolonged sickness response can be deleterious.(Vollmer-Conna et al., 2004) Especially, this unexpected crisis predisposes confirmed cases of COVID-19 to extreme fear of severe disease consequences.(Xiang et al., 2020) Consistent with these viewpoints, depression was an independent risk factor associated with developing severe or critical COVID-19 in our study. In a post-hospitalization COVID-19 study, the patient-perceived recovery was lowest in patients with severe mental and physical health impairment.(Evans et al., 2021) Yet at present we know nothing about any alterations of emotions or cognitive functioning from the direct

effects of the virus on the brain per se, although some patients with COVID-19 were shown to have central nervous system involvement and neurological manifestations.(Asadi-Pooya and Simani, 2020) Our findings suggested that depression may be one of the clues for clinician to estimate the disease progression of patients with COVID-19.

In a previous study, COVID-19 might damage lymphocytes, especially T lymphocytes in patients. The number of T cells significantly decreased, and more hampered in severe cases.(Qin et al., 2020) In this study, patients with depression showed more serious dysregulation in immune system reflected by several laboratory markers mainly including neutrophil, lymphocyte percentage, NLR, T cells count and inflammatory cytokines. Consistent with our findings, another study demonstrated that self-reported depressive symptoms are associated with immune system suppression in patients with COVID-19.(Yuan et al., 2020)

This study has several strengths. The prospective cohort study design allows assessing temporal relationship of mental mood with clinical outcomes and laboratory markers among adult hospitalized patients with moderate COVID-19. In addition, we collected a variety of demographic, socioeconomic, lifestyle factors and therefore were able to control for potential confounding from these factors. There are some limitations. First, this study was based on a major hospital in Wuhan, China. Further investigation is needed to replicate our findings in other settings. Second, the limited sample size in our study precluded further sensitive analysis, while it did not affect the main conclusions of our study. It is a challenge to design a prospective

investigation during the early phase of the emerging infections outbreak. Third, the observational nature of the present study limited the capacity of causal inference.

In summary, this study showed that among patients with moderate COVID-19, depression was independently associated with worse clinical outcomes. Our study proposed an important message to individuals and society that keeping healthy mood might contribute to confront this emerging pandemic and improve clinical outcomes. Early prevention of mental health problems is of vital importance to enhance adherence and improve sleep quality, may help patients have good clinical outcomes and better life quality.

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Contributors: SR, LZ, and WB designed research. TL, SC and ZL contributed to the acquisition, analysis, or interpretation of the data. All authors contribute to critically revise the manuscript for important intellectual content. SR has primary responsibility for final content and is the study guarantor. All authors read and approved the final manuscript. The corresponding authors attest that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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Competing interests: The authors declared no conflict of interest.

Ethical approval: This study was approved by the Medical Ethics Committee of Hubei Integrated Chinese and Western Medicine Hospital.

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Figure legends

Figure 1. Association of HADS-A and HADS-D scores with duration of hospital stay.

Smoothing splines were generated by generalized additive models and adjusted for age, sex, education, smoking, alcohol intake, physical activity BMI, hypertension, diabetes, CVD, and sleep quality. The red line indicates the estimated duration of hospital stay, and the blue dot line indicates 95% confidence intervals.

Figure 2. Association of the HADS scores with risk of progression to severe or critical cases among hospitalized patients with moderate COVID-19.

Table 1. Demographic and Clinical Characteristics of 205 Hospitalized Patients with moderate COVID-19.

	Anxiety		*P-value*	Depression		*P-value*
	yes (n=51)	**no (n=154)**		**yes (n=92)**	**no (n=113)**	
Demographic Characteristics						
Age, y, mean (SD)	60.4 (13.1)	57.1 (13.3)	0.930	6[illegible]9 (12.3)	55.8 (1.3)	0.399
<45	25 (16%)	12 (24%)		[illegible]1 (12%)	26 (23%)	
45-59	57 (37%)	12 (24%)	0.291	[illegible]1 (34%)	38 (34%)	0.052
60-74	59 (38%)	21 (41%)		37 (40%)	43 (38%)	
≥75	13 (8%)	6 (12%)		13 (14%)	6 (5%)	
Male	26 (51%)	80 (52%)	0.[illegible]05	44 (48%)	62 (55%)	0.316
BMI, kg/m^2						
<18.5	5 (10%)	[illegible] (5%)			5 (4%)	
18.5-24	32 (62%)	73 (47%)	0.051	56 (61%)	56 (50%)	0.526
24-27.9	13 (25%)	63 (41%)		31 (34%)	45 (40%)	
≥28	1 (2%)	11 (7%)		5 (5%)	7 (6%)	
Smoker, n (%)	12 (24%)	34 (22%)	0.830	21 (23%)	25 (22%)	0.905
Drinker, n (%)	10 (20%)	29 (19%)	0.903	20 (22%)	19 (17%)	0.372
Frequency of physical activity, n (%)						
Never	20 (39%)	64 (42%)		42 (46%)	42 (37%)	
Sometimes	24 (47%)	43 (28%)	**0.015**	33 (36%)	34 (30%)	0.070
Always	7 (14%)	47 (31%)		17 (18%)	37 (33%)	
Education level						
Less than high school	26 (51%)	65 (42%)		54 (59%)	37 (33%)	
High school	17 (33%)	47 (31%)	0.238	27 (29%)	37 (33%)	**<0.001**
College or higher	8 (16%)	42 (27%)		11 (12%)	39 (35%)	

Good sleep quality, n (%)	1 (2%)	11 (7%)	0.172	1 (1%)	11 (10%)	**0.009**
Clinical Characteristics						
Comorbidities, n (%)						
Hypertension	16 (31%)	48 (31%)	0.953	32 (35%)	32 (28%)	0.485
Diabetes	6 (12%)	21 (14%)	0.441	14 (15%)	13 (12%)	0.314
Cardiovascular disease	3 (6%)	20 (13%)	0.321	11 (12%)	12 (11%)	0.949
Developing severe COVID-19, n (%)	9 (18%)	16 (10%)	0.170	22 (24%)	3 (3%)	**<0.001**
Duration of hospital stay, days	16.8 (9.9)	14.4 (8.2)	0.150	16.8 (9.9)	14.4 (8.2)	0.063

Data are expressed as n (%), mean (SD).

Abbreviations: BMI= body mass index; HADS= Hospital Anxiety and Depression Scale; IL-6= interleukin-6; NLR= neutrophil-to-lymphocyte ratio; SD= standard deviation.

Table 2. Laboratory findings of 205 Hospitalized Patients with moderate COVID-19.

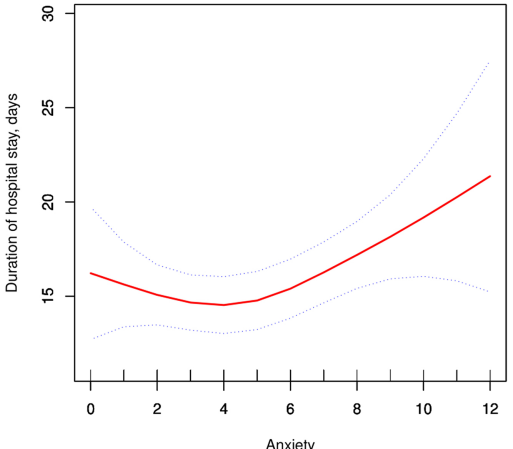
	Anxiety		*P-value*	Depression		*P-value*
	yes (n=51)	**no (n=154)**		**yes (n=92)**	**no (n=113)**	
Blood routine						
White blood cell, g/L	6.4 (2.6)	6 (2.1)	0.288	6.6 (2.7)	5.7 (1.6)	**0.011**
Monocyte percentage, %	7.7 (2.8)	7.3 (2.4)	0.393	7 (2.5)	7.7 (2.5)	0.069
Neutrophil percentage, %	65.1 (14.0)	63.3 (12.6)	0.441	6[illegible].5 (13.5)	61.2 (11.9)	**0.006**
Lymphocyte percentage, %	24.9 (11.7)	27 (10.7)	0.266	24.2 (11.4)	28.6 (10.2)	**0.007**
Neutrophil-to-lymphocyte ratio	2.8 (1.5-4.1)	2.2 (1.6-3.9)	0.429	2.5 (1.6-5.1)	2.2 (1.5-3.2)	**0.016**
Eosinophil percentage, %	1.8 (1.9)	1.9 (1.9)	0.904	1.8 (2.2)	1.9 (1.6)	0.701
Basophil percentage, %	0.4 (0.3)	0.4 (0.3)	0.750	0.4 (0.3)	0.4 (0.3)	0.453
Lymphocyte Subsets						
T cells, /ul	743.5 (307.2)	837.1 (408)	0.341	704.2 (345.4)	905.7 (395.6)	**0.018**
CD4+ T cells, /ul	490.2 (191)	519.1 (243.6)	0.624	457.8 (230.9)	557.7 (221.8)	0.052
CD8+ T cells, /ul	228.3 (146)	287 (219.5)	0.259	231.1 (143.5)	306.5 (240)	0.099
B cells, /ul	149.4 (90)	183.6 (107.6)	0.197	155.3 (95.4)	191.2 (108.9)	0.124
Natural killer cells, /ul	106.8 (54.5)	173.8 (118.4)	**0.015**	121.6 (72.3)	186 (126.5)	**0.008**
Infection-related and hepatorenal function biomarkers						
C-reactive protein, mg/L	3.5 (1.7-29.3)	2.8 (1.8-15.5)	0.437	4.5 (2-49.9)	2.4 (1.7-6.1)	**<0.001**
Serum amyloid A, mg/L	7.4 (1-105.5)	7.5 (1-47.7)	0.921	8.6 (1-183.9)	6.8 (1-18.1)	0.057
Procalcitonin, ng/ml	0 (0-0.1)	0 (0-0.1)	0.085	0 (0-0.1)	0 (0-0)	0.054
Erythrocyte sedimentation rate	21.8 (14.6-37.2)	16.7 (10-41)	0.407	26.5 (15.1-41)	12.1 (8.5-23.8)	**0.004**
D-dimer, mg/L	0.5 (0.3-0.7)	0.4 (0.2-0.7)	0.222	0.5 (0.3-1.1)	0.3 (0.2-0.5)	**<0.001**
Lactate dehydrogenase, U/L	190 (167-232)	190.5 (165-244.5)	0.973	209.5 (173.5-284.5)	186 (157-222)	**0.001**
Alanine aminotransferase, U/L	21 (8-39)	18 (9-32)	0.602	18.5 (7.5-36.5)	19 (10-38.5)	0.403

Creatinine, umol/L	68.7 (56.5-78)	69 (58.3-82.4)	0.717	67.7 (55.2-83.6)	69.8 (59.1-80.6)	0.560
Inflammatory cytokines						
Tumor necrosis factor-α, pg/ml	6.8 (3.6-7.6)	9.2 (6.3-11.9)	0.203	7.6 (5.5-10.3)	8.1 (6.3-15.7)	0.808
Interleukin-6, pg/ml	2.2 (2-6.8)	3.9 (2-14.8)	0.154	5 (2-20.9)	2.6 (2-3.9)	**0.013**
Interleukin-8, pg/ml	8.8 (5.5-12.3)	6.7 (1-11.4)	0.629	7.2 (1-18.2)	7.9 (3.1-10.8)	0.716
Interleukin-10, pg/ml	1 (1-1)	1 (1-1)	0.365	1 (1-5.6)	1 (1-1)	**0.022**

Data are expressed as mean (SD), or median (interquartile range).

Highlights

- Severe pneumonia risk increased fourfold when both anxiety & depression were present
- Depression and anxiety were associated with increased length of hospitalization
- Supporting mental health might improve clinical outcomes following hospitalization


Duration of hospital stay, days
30
25
20
15
0
2
4
6
8
10
12
Anxiety

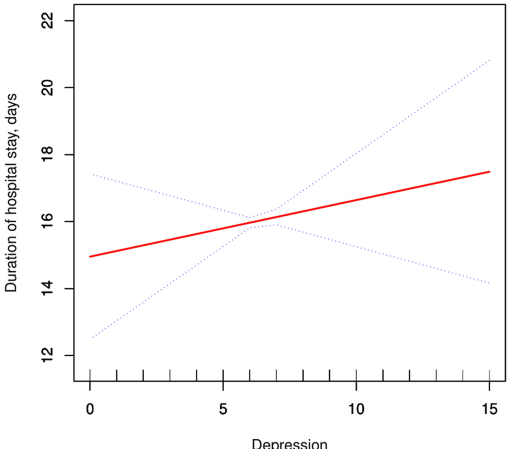
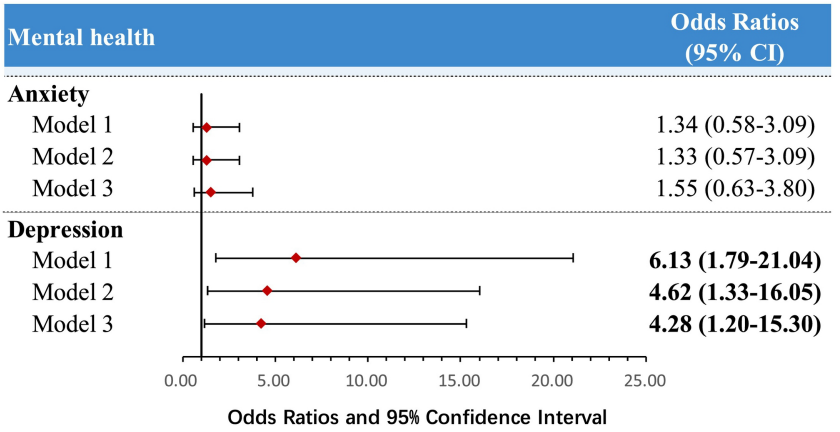
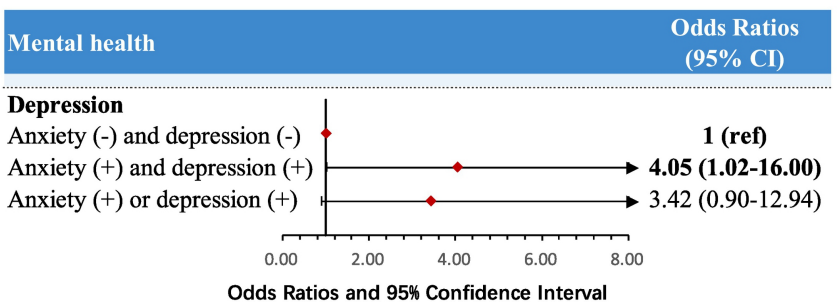

Duration of hospital stay, days
22
20
18
16
14
12
0
5
10
15
Depression

Figure 1



Model 1: adjusted for age, sex.
Model 2: adjusted for model 1 + education, sleep quality, smoking, alcohol intake, and physical activity
Model 3: adjusted for model 2 + BMI, hypertension, diabetes, CVD.



Adjusted for age, sex, education, sleep quality, smoking, alcohol intake, and physical activity, BMI, hypertension, diabetes, CVD.
Horizontal lines represent 95% confidence intervals. CI = confidence interval.

Figure 2